MANUAL

OF

SERUM DIAGNOSIS

BY

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AUTHORIZED TRANSLATION

BY

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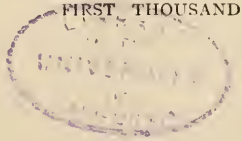
FIRST EDITION

FIRST THOUSAND



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TRANSLATOR'S PREFACE.

Rostoski's Serum Diagnosis, published in the *Würzburger Abhandlungen* in 1903, has become favorably known as one of the best résumés of this subject. In offering this translation attention is called to the fact that several additions have been made in order to include important work done within the past year, viz., Ficker's Typhoid Diagnostic, the test with Formalin Typhoid Cultures, and Para-Dysentery. Most of the material for these additions has been obtained by the translator through personal communication with Dr. Rostoski.

The translator desires to express his thanks to the publishers of the *Würzburger Abhandlungen* for authorizing this translation, also to Dr. Robert J. Wilson of the New York Health Department Research Laboratory, and to the *New York Medical News* for permission to use their cuts illustrating the Gruber-Widal reaction.

Charles Bolduan.

642*a* St. Mark's Ave., Brooklyn,
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SERUM DIAGNOSIS.

CHAPTER I.

GENERAL CONSIDERATIONS.

The bacterial excitants of disease are divided into two large classes. Certain species of bacteria, e.g. the bacilli of tetanus and of diphtheria, do not spread throughout the entire organism, but locate only at their point of entrance into the body, where they develop a poison which reaches the circulation and thus injures the organism. These are called *toxic bacteria* and give rise to the *intoxications*, or *toxæmias*.

Others, on the contrary, e.g. anthrax, typhoid and cholera bacilli, do not give off a poison to their surroundings. They flood the entire body and may locate anywhere and everywhere. When, however, they die and disintegrate, a poison is set free from their bodies which may cause the death of the individual (e.g. in cholera). In speaking of this

group we use the terms *infectious bacteria* and *infectious diseases* or *septicæmias.*

Accordingly, if a bouillon culture of *toxic* bacteria is prepared and then, after several weeks, filtered, it is always possible by means of animal experiments to demonstrate the poison given off by these bacteria. On the other hand the filtrate of a boullion culture of *infectious* bacteria when injected into an animal produces no serious consequences. In this case the poison contained in the body of the bacteria is held back by the filter and becomes free only when the bacteria die and the bacterial bodies disintegrate. In the first group a very small amount of filtrate injected into an animal suffices to excite the entire complex of symptoms of the corresponding disease; in the second case the material left behind on the filter must be used. Corresponding to these two large classes of pathic agents, we distinguish *toxic immunity* and *bacterial immunity.*

The substances by means of which the organism defends itself against the invaders are termed *antibodies.* Not only serum therapy but also serum diagnosis is based upon a knowledge of these bodies. Those concerned in toxic immunity are entirely different from those of bacterial immunity. Against the poisons or *toxins* of bacteria the organism develops *antitoxins;* against the bacteria themselves, *agglutinins* and *lysins.* Nothing is known of

the chemical composition of these bodies, for it has not yet been possible to isolate them from the blood-serum. Ammonium sulphate precipitates the greater part of them in conjunction with those albuminous bodies termed globulins. As shown especially by the researches of v. BEHRING and EHRLICH, antitoxins possess the property of neutralizing toxins, i.e. to prevent their poisonous action on the animal organism. For example, by injecting an animal with gradually increasing doses of toxin, and so causing antibodies to be produced, it is possible finally to inject a dose of toxin which before would certainly have caused the death of the animal. But even when an antitoxic serum is mixed with toxin in a test-tube and the mixture then injected, the animal will live, whereas a similar animal injected only with the toxin will die. We now believe that the action whereby the poison is made innocuous depends on purely chemical processes and that the organism has no part therein.

The bacteriolysins and the agglutinins, as already mentioned, are developed by the infected body itself as a defense against the invasion of bacteria. The former have the property of dissolving the bacteria; the latter, of clumping them together into little masses.

The bacteriolysins were discovered by PFEIFFER. The experiment by means of which they can be

demonstrated is as follows: Cholera immune serum is mixed with cholera bacilli, and the mixture is introduced into the peritoneal cavity of a guinea-pig. From time to time small quantities of the mixture are withdrawn by means of capillary glass tubes, and it is seen that in the peritoneal juices the bacteria undergo destruction in a peculiar manner. They lose their motility almost immediately, commence to swell in about ten minutes, disintegrate into little granules, and finally in about half to one hour nothing more is to be seen of them. As a result of the bacteriolysin present in the serum, they have been dissolved. The animal survives, whereas control animals which received no immune serum with the injection of the bacteria die. Until recently it was believed that the lysins acted only in the living organism, as, for example, in the peritoneal cavity of the guinea-pig in the above experiment. The same solvent action on bacteria can, however, be observed in a test-tube when *perfectly fresh* immune serum is used. The bacteriolysins are characterized by a high degree of specificity. Cholera immune serum dissolves only cholera bacilli, typhoid immune serum only typhoid bacilli, etc.

The agglutinins were discovered by GRUBER and DURHAM. They can be observed either in a test-tube or in a microscopical preparation. For example, if typhoid or cholera immune sera are added respectively

to a 24-hour culture of typhoid or cholera bacilli, and the mixture placed into a thermostat, the following phenomenon will be noticed: The bacteria which previously clouded the bouillon uniformly, clump together into little masses, settle to the sides of the test-tube and gradually fall to the bottom until the fluid is almost entirely clear. In a control test, on the contrary, to which no active serum is added the fluid remains uniformly cloudy. The reaction is completed in twenty-four hours at the most. If the reaction is observed in a hanging drop, it is seen that the addition of the active serum first produces an increased motility of the bacteria which lasts a short time and is followed by a gradual formation of clumps. One gets the impression that the bacteria are dying together. Frequently one sees bacteria which have recently joined a group make violent motions as though they were attempting to tear themselves away; then they gradually lose their motility completely. Even the larger groups of bacteria may exhibit movement as a whole. After not more than one or two hours the reaction is completed; in place of the bacteria moving quickly across the field, one sees one or several groups of absolutely immobile bacilli. Now and then in a number of preparations one sees a few separate bacteria still moving about among the groups. If the reaction is feeble, either because

the immune serum has been strongly diluted or because it contains very little agglutinin, the groups are small and one finds comparatively many isolated and perhaps also moving bacteria. It is essential each time to make a control test of the same bacterial culture without the addition of serum. Under some circumstances the reaction proceeds with extraordinary rapidity so that the bacilli are clumped almost immediately. By the time the microscopical slide has been prepared and brought into view nothing is to be seen of any moving or isolated bacteria, and only by means of the control test is it possible to tell whether the culture possessed normal motility. We are not yet informed as to the nature of these phenomena. A number of theories has been advanced, into which, however, we cannot here enter.

In some cases the agglutinins are active even in very high dilutions. Thus in typhoid patients and typhoid convalescents a distinct agglutination has been observed in dilutions of 1:5000, and this action persisted for years, though not, of course, in the same degree. Even normal blood-serum, when undiluted, often produces agglutination. But the above specific agglutinins, which do not exist beforehand, being formed only in consequence of an infection, are characterized by this, that the agglutination occurs even when the serum is diluted

(at least 1:30 to 1:50), and, furthermore, that after this dilution the action is still specific, i.e. cholera immune serum agglutinates only cholera bacilli, typhoid immune serum only typhoid bacilli, etc. This specificity, however, as will be shown later, is not always absolute.

The agglutinating substances when mixed with bacteria are bound by these, the two bodies effecting a loose combination very like toxin and antitoxin. By chemical means it is possible to again separate the agglutinin from the bacteria and use it to agglutinate bacteria anew.

It was formerly assumed that agglutination was a *prerequisite for bacteriolysis*. This, however, is not so, for both in cholera and in typhoid immunity bacteriolytic substances have been observed without agglutinins, and agglutinating substances without bacteriolysins.

Of the three antibodies mentioned, serum therapy has thus far made use of the antitoxins, whereas in serum diagnosis the bacteriolysins and above all the agglutinins are used. *Serum diagnosis by means of these two substances was possible only because they had proven themselves in general as specific.*

Besides the antibodies formed against bacteria and the products of bacterial metabolism a whole series of other antibodies has been discovered and experimentally demonstrated. Some of these have

also found application in serum diagnosis. For example, an animal organism injected with cells of the greatest variety develops clumping and dissolving substances, *cyto-agglutinins* and *cytolysins*, which, analogous to the antibodies acting on bacteria, agglutinate and dissolve these cells. A special form of cytolysis and one which has been particularly studied is that affecting the red blood-cells and termed *hæmolysis*. Against ferments, *antiferments* are developed, and these inhibit the action of the former or weaken it Finally, if we inject an animal with albuminous bodies of the greatest variety, substances will appear in the blood which possess distinct relations to these bodies. They manifest themselves by their power to precipitate the albuminous bodies from dilute solutions in a test-tube These antibodies are therefore called *precipitins* (BORDET, TCHISTOWITCH). A phenomenon discovered by R. KRAUS [1] is probably to be separated from this precipitin action on albumins. This author showed that the serum of a rabbit immunized against typhoid produces a precipitate in the bacterial-free filtrate of a bouillon typhoid culture. This fact has been verified by a number of investigators and found to extend also to other species of bacteria.

[1] Über spezifische Reaktionen in keimfreien Filtraten aus Cholera-, Typhus- und Pestbouillonkulturen. *Wiener klinische Wochenschrift* 1897, No. 32.

A diagnostic procedure studied by SCHOTTMÜLLER[1] also deserves mention. This author abstracts 20 c.c. blood by means of a needle and glass syringe from one of the veins at the elbow and then by means of cultures seeks to demonstrate the excitant of the disease. The blood is apportioned among tubes each containing 5 c.c. of agar previously fluidified and cooled to 45° C. The mixtures are then carefully shaken and plated. SCHOTTMÜLLER'S results are especially favorable in typhoid, for he succeeded in 84% of the cases in demonstrating typhoid bacilli in the blood of the patients. In some instances this result was achieved as early as the first day of illness. In this method, then, the excitants of the disease are demonstrated in the blood-serum or plasma, and one could therefore term this procedure a method of serum diagnosis. This term, however, has gradually come to be restricted to those procedures in which the antibodies are employed. Hence, although SCHOTTMÜLLER'S method is full of promise, I have merely mentioned it and shall discuss it no further. I should like to observe, however, that the spirilla of relapsing fever can be demonstrated directly in the blood simply by microscopic examination of the unstained preparation, while the malarial parasites

[1] Zur Pathogenese des Typhus abdominalis. *Muenchener med. Wochenschrift* 1902, No. 38.

can be similarly observed, but in the red blood-cells.

Of the two antibodies concerned in bacterial immunity the agglutinins have till now been given the preference in serum diagnosis. And just as serum therapy has achieved such success with one particular disease, serum diagnosis has proven of great value in another, namely, typhoid. In this it has gained an assured place among the diagnostic methods of the physician and added materially to his diagnostic resources.

CHAPTER II.

TYPHOID AND PARA-TYPHOID.

The Gruber-Widal Reaction.—The serum diagnosis of typhoid by means of the agglutinins was introduced chiefly through the labors of GRUBER and WIDAL. The studies undertaken by GRUBER and his pupil DURHAM began as early as 1894. At the Congress for Internal Medicine in 1896 [1] GRUBER first announced that he had discovered the reaction in typhoid convalescents, and asked that his observations be verified if possible. Soon after this PFEIFFER and his co-workers published a study which confirmed GRUBER's results.[2] The significance of the reaction as a diagnostic help was unquestionably first pointed out by WIDAL, who showed that the reaction appears at a relatively early period of the disease and may therefore be employed as a diagnostic measure.[3] We must not omit to state that GRÜNBAUM in March 1896, several months before

[1] Transactions of the Congress, edited by E. von Leyden and R. Pfeiffer, Wiesbaden, 1896.

[2] Pfeiffer and Kolle, *Deutsche med. Wochenschrift* 1896, No. 12.

[3] *Bulletin de la soc. méd. des hôp.*, June 26, 1896.

WIDAL's publication, had also grasped the significance of the reaction as a diagnostic measure.[1] Owing to insufficient clinical material his publication did not appear until some time after WIDAL's. Hence, in acknowledgment of the labors of the two authors most concerned in the discovery and introduction of this reaction, we now speak of it as the "GRUBER-WIDAL reaction," whereas in the beginning only the term "WIDAL reaction" was used.

The manner in which the reaction proceeds in microscopical preparations as well as when macroscopically observed has been described above (page 5). Nowadays the microscopic method is given the preference because in many cases it is distinct when the macroscopic reaction fails; and further because the former yields distinct results within an hour at the most, whereas in many cases twenty-four hours are required for the macroscopic test. So far as the technique of the method is concerned it is best to use a fresh (12–20 hrs.) typhoid culture, an agar culture mixed with either bouillon or physiological salt solution, or a buillon culture. In all cases a control preparation is to be made of the culture and observed, for in bouillon cultures one often sees that the typhoid bacilli lie

[1] *Lancet*, Sept. 19, 1896; *Muench. med. Wochenschrift* 1897, No. 13; Blood and the identification of bacterial species, *Science Progress*, Vol. I, No. 5, 1897.

together in the form of little clumps even before the serum is added.[1] This of course makes it more difficult to decide whether or not there is any reaction, and in some cases makes the entire culture valueless for the test. In such cases it is absolutely essential to employ an agar culture mixed with 0.85% salt solution. But according to WIDAL [2] it is possible to observe the phenomenon of agglutination not only in fresh, but also in dead cultures. WIDAL and PROESCHER [3] have therefore recommended the employment of cultures which have been killed with formalin. Working with such cultures has the advantage that any physician can perform the test himself, without the aid of a bacteriological laboratory, so long as he has a microscope with an oil-immersion objective.

Most authors, however, prefer fresh bouillon or agar cultures to dead ones. As a rule any laboratory culture can be used for the reaction, although differences in respect to slower or quicker agglutination are met with. The reason for these differences is not yet clear. It is especially mentioned

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[1] This is more apt to be the case when the culture is over twenty-four hours old.—C. B.

[2] *Comptes rend. des Séances de la Soc. de biol.*, Paris, Jan. 30, 1897.

[3] Proescher, Zur Anstellung der Widal'schen Reaction, *Centralblatt für Bacteriologie*, Vol. XXXI, No. 9. 1902. See also page 44.

that bacilli freshly cultivated out of the body frequently do not agglutinate, either with serum from the same patient or from other typhoid patients.[1] It is best, therefore, to prepare the culture to be used in the reaction by transplanting from an older laboratory culture. STERN makes the interesting statement that a number of otherwise similar typhoid colonies were grown from the serum of a typhoid patient, of which, however, only a part were agglutinated by the serum of this patient. In the same way these colonies were variously affected by other typhoid sera.[2]

As already mentioned, undiluted serum must not be employed for this test, for under some circumstances even normal serum or the serum of patients suffering from a disease other than typhoid will agglutinate when used in strong concentrations. However, it appears to me that this agglutination by the serum of healthy individuals is much less frequent than would appear from the statements of various authors. I have examined a whole series of healthy individuals in whom even with a dilution of 1:5 no agglutination was demonstrated. In his first communication WIDAL mentioned 1:10 as a suitable dilution; later on the limit was fixed

[1] Compare Müller, Paul Theodor, Über die Immunisierung des Typhus bacillus gegen specifische Agglutinine. *Muench. med. Wochenschrift* 1903, No. 2.

[2] *Berliner klin. Wochenschrift* 1903, No. 30.

at 1:30; and now for some years a reaction must be produced with a dilution of 1:50 in order to be conclusive (STERN). I should like to add that even with this dilution the reaction must be *strongly marked*, i.e. when the preparation is kept in a thermostat, large clumps must be demonstrable within half an hour at the most, and no separate bacilli must lie between these clumps. Preparations in which after a considerable time only small groups of four to six bacilli are formed and in which a large number of bacilli are not agglutinated may be of value in determining the limits of the agglutinating power of the serum. In this dilution, however, such reactions are no longer conclusive for the diagnosis of typhoid. At least this is my experience.

The most convenient method of procedure is to prepare the dilution of blood by means of the mixing-pipette used for counting white blood-cells which is found in the THOMA-ZEISS blood-counting apparatus.[1] According to the method described by me,[2] one lances the finger-tip or the ear and draws the blood into the pipette to the mark 0.5. Then *distilled water* is sucked up as far as the mark

[1] Pfaundler, Meinhard, Eine handliche Methode zur Messung der agglutinations Fähigkeit des Blutes Kranker. *Wiener klin. Wochenschrift* 1898, No. 21.

[2] Rostoski, Zur Kenntniss des Typhus renalis, *Muench. med. Wochenschrift* 1899, No. 7, page 212.

11. In this way we have prepared a dilution of blood of 1:20, and of blood-serum of 1:30. Furthermore, the blood has become laky so that the red blood-cells do not disturb the observation. One loop of this dilution is now mixed on a cover-glass with one loop of typhoid culture, thus making a dilution of the serum of 1:60. A positive reaction in this case can therefore be regarded as diagnostic. The preparation thus made is immediately looked at in a hanging drop and again after half an hour, during which time it is kept in an incubator. In case of a marked reaction either complete agglutination or the commencement of the same is observed almost *immediately;* in other cases, after the lapse of half an hour. If the preparation is not kept in the incubator, one must wait three-quarters to one hour before proceeding with the second observation. The above method avoids, above all, sucking up the typhoid culture, a practice against which I should like to warn, for a number of accidents have already been caused thereby.

As already mentioned, according to my experience the reaction with this dilution must be strongly marked in order for it to be regarded as diagnostic of typhoid.[1] Large groups or clumps must have been formed, and only here and there should an

[1] See Wilson's study reproduced in the Appendix, page 81.

isolated non-agglutinated bacillus be seen. If it is desired to find the limits of the agglutinating power, one proceeds as follows: By means of the mixing-pipette new dilutions are prepared from the first dilution. Thus, by sucking up this blood dilution to 0.5, 0.4, 0.3, 0.2, 0.1 and diluting fluid (85% salt solution) to the mark 1. and then proceeding as before, dilutions will be obtained of 1:120, 1:150, 1:200, 1:300, and 1:600 respectively. If higher dilutions are required, the diluting fluid must be sucked up to the mark 11. These preparations are likewise observed immediately, then placed into the incubator and observed again one hour afterward.[1] The limit is regarded as the dilution in which small clumps (four to six bacteria) are formed even though the majority of bacteria are not at all agglutinated. Naturally, in this case the control preparation must be free from clumps. The immobilization of the bacteria which occurs with agglutination is entirely irrelevant so far as judging the result of the reaction. Motility of the bacteria is not at all necessary for the occurrence

[1] The limits of the agglutinating power may vary somewhat according to the time limit employed in observation. I regard one hour as entirely sufficient for this; in rare cases a few groups may still be formed after this time. Above all it is important always to employ the same time limit in determining the limit of agglutination. If the preparations are not kept in the incubator, the time must be extended somewhat, about 1½ hours.

of agglutination. The importance of determining the limits of the agglutinating power was first emphasized by STERN.[1] It is especially valuable scientifically.

WIDAL first pointed out that serum was not absolutely essential for the test bearing his name, but that blood (even old dried blood) would suffice.[2] As the reaction is described above we make use of the blood directly. This has the advantage that one is able to perform the test at once without waiting for the serum to separate. In the above method, however, we are unable to employ dilutions less than 1:60, for the blood-cells will not dissolve if the blood is drawn up into the mixing-pipette higher than the mark 0.5. If, therefore, we wish to use smaller dilutions, or if the test is not required at once, we may proceed as follows: A little blood is caught up in a small sterile test-tube about 8 cm. high and 1 cm. in diameter. The patient's arm is first allowed to hang out of the bed so as to cause slight stasis, the finger-tip is then lanced and the flow of blood assisted by milking the finger. In this way it is very easy to collect one-half to one c.c. of blood. Venesection is not at all required. The clot which at once forms is detached from the sides of the tube with a needle and the tube then placed

[1] Über Fehlerquellen der Serodiagnostik, *Berl. klin. Wochenschrift* 1897, No. 12.

[2] *Comp. rend.* June 26, 1896.

on ice until the following day to allow the serum to separate, or separation is effected by means of the centrifuge. The dilution is again effected by means of the mixing-pipette or of a uniform capillary tube on which marks have been made with the aid of a centimeter measure. The pipette of a GOWER'S hæmoglobinometer is also very useful for this purpose (STERN).

So far as the clinical value of the GRUBER-WIDAL reaction is concerned, the following points are important: *How early the reaction appears, whether it is found only in typhoid, and finally whether it is found in every case of typhoid or is occasionally absent.*

When the Reaction Appears.—An early appearance of the reaction would be especially important. It is just in the beginning of the disease that the diagnosis is often extremely difficult, because as a rule the classical symptoms gradually develop only in the course of the second week. The reaction is first observed on the fourth to the seventh day of the disease. A still earlier appearance is to be regarded as a great rarity, though such cases have been reported. Thus C. FRAENKEL, JOHNSTON and TAGGART even report a positive reaction on the second day of the disease, and F. PICK and KÖHLER one on the third day.[1] LEVY, out of thir-

[1] Compare Köhler, *Klinisches Jahrbuch* 1902, pp. 52 and 53.

teen cases, found a positive reaction in the first week in ten of these.[1] According to ULLMANN and WÖHNERT half of the cases examined by them show a positive reaction with a dilution of 1:40 even in the first week.[2] According to my own experience and that of other authors a positive reaction in the first week is not so frequent, especially when dilutions of 1:50 are employed. In many cases, to be sure, I obtained a positive reaction on the fifth to the seventh day, that is at the end of the first week, but in most of the cases a positive reaction was not obtained until the course of the second week. After this, that is, during the third and fourth weeks and during convalescence, the development of the reaction is less frequent In this all authorities agree. VON LEUBE, for example, reports a case in which the reaction appeared first on the eighteenth or nineteenth day of the disease after the patient had already had an intestinal hemorrhage. Had he died of this we should have had a case of typhoid without a GRUBER-WIDAL reaction.[3] RUMPF[4] mentions two cases in which the reaction appeared on the 59th and 97th days respectively. Recently I myself saw a case in

[1] *Wiener klin. Wochenschrift* 1897, No. 33.

[2] *New York Medical Journal*, Feb. 20, 1897.

[3] *Muench. med. Wochenschrift* 1898, No. 8.

[4] Über den Typhus abdominalis, *Berl. klin. Wochenschrift* 1900, No. 24.

which the reaction did not appear until after the third day of normal temperature. In passing it may be remarked that *absolutely no prognostic* conclusions can be drawn from the earlier or later occurrence of the reaction or from the intensity of the same. From the preceding it follows *that the* GRUBER-WIDAL *reaction permits us in some instances to make the diagnosis of typhoid when the rest of the typhoid symptoms still fail us (during the first week of the disease). In most cases, however, it constitutes the most important symptom of typhoid in the second week and less frequently still later.*

The Reaction in Conditions other than Typhoid.—In considering the question as to whether the reaction occurs only in typhoid, regard must be paid to the fact that the reaction can persist a very long time after recovery from the disease. UNVERRICHT observed the reaction in one case twenty-one years after the illness, and in two-thirds of all his cases five years afterward.[1] Other authors, however, mention a shorter duration of the reaction. According to COURMONT,[2] in children the reaction disappears within the first two months; in adults in four or five months. He was able to find the reaction in only two cases out of fourteen at the end

[1] Handbuch der prakt. Medizin, edited by W. Ebstein, Vol. V. p. 352.

[2] *Semaine Médicale* 1897.

of one year. KASEL and MANN [1] likewise emphasize that the reaction disappears especially rapidly in children. According to KÖHLER,[2] only a comparatively small percentage of patients still show the reaction after a year. My own experience coincides with KÖHLER's. It is certainly rare that the reaction remains for only two weeks after subsidence of the fever, though I have seen even such cases. From what has been said it follows that a patient suffering from an acute infectious disease may show a GRUBER-WIDAL reaction which is due to a previous typhoid; and if that should have been a very mild or walking typhoid or one that was not recognized, the patient would be entirely ignorant of the attack. Hence VON LUEBE [3] states that the reaction is especially conclusive when after being negative in the beginning of the disease it becomes positive some time after.

Quite independently of these patients who have previously had typhoid, there are sick and healthy persons in whom a GRUBER-WIDAL reaction is demonstrable. Foremost to be considered is the fact that the serum of jaundiced patients frequently agglutinates typhoid bacilli, as was first shown by

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[1] Beiträge zur Lehre der Gruber-Widal'schen Serumdiagnose des Unterleibs-typhus, *Muench. med. Wochenschr.* 1894, No. 18.

[2] l. c. p. 81.

[3] l. c.

GRÜNBAUM.[1] He also showed a similar action on cholera bacilli. The agglutination of typhoid bacilli by icteric serum has recently been thoroughly studied by a number of authors. The studies of KÖHLER,[2] ECKHARDT,[3] ZUPNIK,[4] MEGELE,[5] R. STERN,[6] and JOACHIM[7] especially deserve mention. These show that the serum of icteric patients agglutinates typhoid bacilli in a fairly large percentage of cases, even if not so regularly as that of typhoid patients. LÜDKE, in a study at the medical clinic at Würzburg, found seventeen out of thirty cases of jaundice to possess agglutinating action with a dilution of 1:20, though only in nine cases when he used dilutions of 1:50, a dilution equal to that employed in typhoid diagnosis. KÖHLER found six cases out of eight, but here stronger concentrations were used. It is seen, therefore, that the agglutinating phenomenon is not uniform in its appearance. On the other hand the agglutination may be very pronounced. I observed one case of catarrhal jaundice

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[1] Grünbaum, Über den Gebrauch der agglutinierenden Wirkung von menschlichem Serum für die Diagnose des Abdominaltyphus. *Muench. med. Wochenschrift* 1897, No. 13.

[2] l. c. and *Muench. med. Wochenschrift* 1903, No. 32.

[3] *Muench. med. Wochenschrift* 1902, No. 27.

[4] *Ibid.*, 1902, No. 31.

[5] *Ibid.*, 1903, No. 14.

[6] l. c.

[7] J. Joachim, Vienna, Zur Frage der Gruber-Widal'schen Reaktion bei Ikterus, *Wiener klin. Wochenschrift* 1903, No. 35.

in which agglutination was still very marked in dilutions of 1:1000, and ECKHARDT reports two cases of Weil's disease in which the serum possessed equally strong agglutinating power. The cause of the jaundice seems not to have much bearing on the subject; agglutination has been found in all forms of jaundice. By investigating a large number of bacteria, LÜDKE has demonstrated that in many cases the agglutination affects only typhoid bacilli. Nevertheless it must be remembered that now and then other varieties of bacteria are agglutinated, such as *proteus* and *bacterium coli*. Unfortunately it is not yet clear to what these curious phenomena are due. The agglutination cannot be due to the bile as such, for this, as LÜDKE could prove, usually does not agglutinate at all. Furthermore ECKHARDT has described a case in which the icteric serum agglutinated, while the bile obtained through a biliary fistula did not. And yet the bile when absorbed into the blood-serum could so change the latter that it gained agglutinating power. Experimental researches in this direction, however, have not been entirely successful. Thus LÜDKE was never able to produce any agglutinating property in serum by mixing serum with bile in a test-tube, or by injecting bile into an animal. KÖHLER, however, by injecting one of the bile constituents, namely taurocholic acid, intravenously into a dog

and by tying off the *ductus choledochus* succeeded in producing an agglutinating property in the serum. We are not yet clear as to the nature of the changes caused by the bile in the serum. It must not be forgotten that in a great many cases of jaundice (catarrhal jaundice, Weil's disease, abscess of the liver) we are surely dealing with an infection, and that probably in other cases an infection exists along with the jaundice. Now it has been shown that, following the infection with one species of bacterium, the agglutination affects not only this, but also certain other species. Paratyphoid and several kinds of coli bacteria are in some cases agglutinated by typhoid serum. *Proteus* and *staphylococci* may even give rise to an agglutinin acting on typhoid bacilli.[1] In general the serum agglutinates most strongly the infecting micro-organism, though stronger agglutination of a different bacterium has been observed (De NOBELE[2] and others). We may therefore assume that an infection very often occurs in jaundice and that the infecting micro-organism produces an agglutinin which acts also on typhoid bacilli. Hence the infection need not necessarily be with typhoid. This explanation of the frequent agglutination observed

[1] Lubowski and Steinberg, cited by Stern.

[2] De Nobele, Le sérodiagnostic dans les affections gastro-intestinales d'origine alimentaire, 2me mémoire, 1901. Cited by Stern, l. c.

with the sera of jaundiced patients has been especially urged by STERN.[1] Basing my conclusions on personal observations, I must express my agreement with this view, at least for a large number of cases.

In the same way it may be possible to explain the cases other than jaundice, during the course of which the serum acquires agglutinating properties for typhoid bacilli. Thus LOMMEL,[2] for example, has published a case of puerperal fever (verified by necropsy) in which there was a marked GRUBER-WIDAL reaction. Altogether, however, the number of observed cases is not large. *In my opinion, therefore, when a strongly positive* GRUBER-WIDAL *reaction is present (excepting in jaundice), and the other symptoms do not point to an abdominal typhoid, one should always think of an unusual localization of the typhoid process (pleuro-, pneumo-, nephro-typhoid, etc.), or that an infection with typhoid bacilli exists with some other disease.* As an example, I should like to call to mind the case published by me in which, beside vague symptoms and high fever, a hæmorrhagic nephritis occurred.[3] The GRUBER-WIDAL reaction was strongly positive, and this was the first to excite suspicions of a typhoid infection.

[1] l. c.

[2] Lommel, Eine Fehldiagnose auf Grund der Gruber-Widal-'schen Reaktion, *Muench. med. Wochenschrift* 1902, p. 314.

[3] *Muench. med. Wochenschrift* 1899, p. 209.

Seven days later it was possible to demonstrate typhoid bacilli in the urine, and the disease began more and more to assume the course of true typhoid. In the same way in the case reported by DIEUDONNÉ and RÖPER [1] the GRUBER-WIDAL reaction called attention to the fact that the existing pneumonia was typhoid in character. Thereupon the typhoid bacilli were found in the sputum. Similarly in the two cases of pneumonia reported by KASEL and MANN [2] I should assume that an unusual localization of the typhoid poison is not to be denied offhand. A case described by PECHÊRE and HEGER [3] shows that great caution should be exercised here. The subject was a consumptive in whom a typical typhoid with a positive GRUBER-WIDAL reaction developed. At the post-mortem examination no typhoid changes were found in the intestine, only tubercular lesions (miliary tubercles on the mucous membrane of the ileum), and the entire complex of symptoms was about to be regarded as that of miliary tuberculosis. But that typhoid was nevertheless present was shown by the presence of typhoid bacilli in the spleen.

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[1] l. c. Würzburg, 1901.

[2] l. c.

[3] Sérodiagnostic de Widal positiv dans un cas mortel de tuberculose aigne avec autopsie. *Journ. méd. de Bruxelles* VIII, 1899. Cited by Unverricht, Abdominal Typhoid, in Ebstein's Handbuch der prakt. Medizin, Vol. V. page 352.

Failure of the Reaction.—Coming now to the question whether, under all circumstances, the reaction must develop in typhoid, we must regretfully answer in the negative. Positive cases of abdominal typhoid have been described in which a GRUBER-WIDAL reaction did not develop. In some of these cases the diagnosis was confirmed by autopsy, for example in the two cases reported by REISSNER.[1] Since the agglutinating property of the serum sometimes develops very late, one could of course say that in these cases, if the patient had lived, the reaction would have developed toward the end of the illness or during convalescence. Hence only a case in which the patient recovered and the typhoid bacteria were demonstrated will be conclusive. By means of SCHOTTMÜLLER'S procedure already mentioned, it is now much easier than formerly to demonstrate the typhoid bacilli in the blood, and by means of the culture medium devised by VON DRIGALSKI and CONRADI the same holds true for the bacilli in the fæces. Cases in which EBERTH'S bacilli were present although the GRUBER-WIDAL reaction was negative have been collected from the earlier literature by VON HOFFMANN.[2] Especially convincing are the statistics published by

[1] Ein Beitrag zur Würdigung der Gruber-Widal'schen Reaktion des Abdominaltyphus, Leipzig, 1898.

[2] *Hygienische Rundschau* 1902, No. 17.

JÜRGENS,[1] for in this the paratyphoid bacillus has been regarded. I think, however, that we should not extend our scepticism too far; and that we may include several earlier described cases which ran a typical typhoid course. Thus I observed one case in which not only all the classical symptoms of abdominal typhoid were present, but also a series of complications especially characteristic of this disease: intestinal hæmorrhage, pneumonia, and the formation of abscesses and furuncles during convalescence. Nevertheless the GRUBER-WIDAL reaction remained negative throughout the entire course of the disease and during convalescence. Nor were paratyphoid bacteria (see below) agglutinated. According to the opinion of almost all authorities the absence of a GRUBER-WIDAL reaction in typhoid is nevertheless very infrequent. Among 220 cases occurring in the medical clinic at Würzburg I saw only three cases in which the reaction was entirely absent. Yet in the last 180 cases we regarded only those reactions as positive which developed quickly and with a dilution of 1:60. With the first forty patients, corresponding to the general opinion at that time, we held that a dilution of 1:33 was sufficient. In numerous cases the limits of the agglutinating power were determined.

[1] *Zeitschrift für Hygiene und Infectionskrankheiten*, June 1903, page 372.

They showed, in part, agglutinating values of 1:800 to 1:1000, but this cannot be further discussed here. Other authors have had analogous experiences. KÖHLER examined a series of 88 cases and found only one with a permanently negative reaction; WIDAL noted one failure in 177 cases; MARIOTTI, four out of 218 (dilution 1:40); KASEL and MANN, two out of 43 cases at the polyclinic at Würzburg. According to the statistics collected by v. HOFMANN,[1] out of 2595 cases, 170 (=6½%) showed no GRUBER-WIDAL reaction.

Paratyphoid.—It is possible that the cases of typhoid heretofore described as giving no GRUBER-WIDAL reaction were to a large extent cases of *paratyphoid.* As is well known, this is the name by which we now, in conformity with SCHOTTMÜLLER,[2] designate an infectious disease which is produced not by the typhoid bacillus but by one closely related to this which stands about midway between *B. typhosus* and *B. coli.* During the course of the investigations it has been found necessary to distinguish two varieties, *type A* and *type B*, which differ also in their agglutinating property. It

[1] Zur Frage des Paratyphus mit besondere Berücksichtigung der bei ihm fehlenden Gruber-Widal'schen Reaktion. *Hygienische Rundschau* 1902.

[2] Über mehrere das Bild des Typhus bietende Krankheitsfälle, hervorgerufen durch typhusähnliche Bacillen. *Zeitschr. f. Hygiene and Infectionskrankheiten* 1901, No. 36; *Deutsche med. Wochenschrift* 1900, p. 511.

remains to be seen whether we shall have to differentiate any additional types. There are no certain distinguishing features to separate the clinical pictures of abdominal typhoid and paratyphoid. Many cases of paratyphoid present all the classical symptoms of typhoid. According to CONRADI, v. DRIGALSKI, and JÜRGENS [1] the fever curve of paratyphoid is characterized by a fairly sudden rise, an irregular course of the temperature with almost always an absence of the continua. Besides this, the disease has a better prognosis and a slow convalescence. According to other authors, the enlargement of the spleen is quite often absent (DE FEYFER and KAYSER [2] missed it in 42% of the cases), whereas an involvement of the upper portions of the intestinal tract (gastric fever!) is more common.[3] Further than this it is unwise to lay much stress on peculiarities in the course of the disease, for we know that true typhoid runs a variable course. We have only to think of the vast difference between a mild or abortive typhoid and a fully developed or, better still, a complicated case.

[1] Über eine unter dem Bilde des Typhus verlaufende, durch einen besonderen Erreger bedingte Epidemie. *Zeitschrift für Hygiene und Infectionskrankheiten* 1903, No. 42, page 41.

[2] Eine Endemie von Paratyphus, *Muench. med. Wochenschr.* 1902, p. 1692.

[3] Über eine Erkrankung mit dem Befund eines typhusähnlichen Stäbchens im Blute (Paratyphus), *Muench. med. Wochenschrift* 1902, page 11.

It will almost always be impossible to separate a case of true typhoid from a paratyphoid by the symptoms alone. At the most, during an epidemic the general course of the disease, when it agrees with the above points, may cause one to suspect paratyphoid. SCHOTTMÜLLER and KURTH,[1] from a total of 180 cases which had been looked upon as typhoid, were able in twelve cases to isolate a paratyphoid bacillus.

HÜNERMANN[2] observed a whole epidemic in which typhoid-like bacteria were found in the blood, which he regarded as the cause of the disease. The GRUBER-WIDAL reaction 1:100 was positive in only 42%; the newly found bacillus was always agglutinated. Similar reports concerning an epidemic of fourteen cases in Holland are made by DE FEYFER and KAYSER;[3] and SION and NEGEL[4] report one from Roumania. Formerly none of these cases would have been differentiated from true typhoid.

In connection with the serum reaction in paratyphoid, it should be remembered that very often the bacilli of typhoid, of paratyphoid type A,

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[1] Über typhusähnliche, durch einen bisher nicht beschriebenen Bacillus bedingte Erkrankung. *Deutsche med. Wochenschrift* 1901, Nos. 30 and 31.

[2] *Zeitschrift für Hygiene*, Vol. XL. page 522.

[3] l. c.

[4] *Centralblatt für Hygiene*, Vol. XXXII. page 481.

and of paratyphoid type B produce each a specific agglutination, i.e. the serum of a patient infected with paratyphoid type A will agglutinate only paratyphoid bacilli type A, and not those of type B nor those of true typhoid. The bacilli of typhoid and of paratyphoid type B behave similarly *In practice, therefore, all cases suspicious of typhoid which do not agglutinate typhoid bacilli should be examined also with paratyphoid bacilli of both types.*[1] If this is done, cases of typhoid without a GRUBER-WIDAL reaction will certainly become less frequent. The case cited above, in which, although typical typhoid symptoms were present, I could obtain no agglutination either with typhoid or paratyphoid bacilli, is not absolutely conclusive, for the reason that the agglutination test for paratyphoid was only undertaken several weeks after the subsidence of the fever. During this time an agglutinating action possessed by the serum for these bacteria might have been lost.

Group Agglutination.—If a typhoid or paratyphoid serum possess a high degree of activity, i.e. ability to agglutinate even in large dilution, it may happen that with lesser dilution it may also agglutinate the two related bacilli. Thus, in two cases reported by DE FEYFER and KAYSER,[2] the infecting para-

[1] See page 86.

[2] l. c.

typhoid bacilli type B were agglutinated 1:5700; typhoid bacilli, however, only 1:120, while paratyphoid bacilli type A were not agglutinated at all. According to BRUNS and KAYSER,[1] the maximum limits of agglutination for the infecting and the related bacteria differ by twenty times or over. When these values approach each other markedly, a mixed infection should be suspected, i.e. an infection with several species of bacteria. In examining the serum of typhoid patients possessing high agglutinating power for typhoid bacilli, I made use of two paratyphoid cultures (both types) kindly placed at my disposal by SCHOTTMÜLLER. In six cases, although typhoid bacilli were agglutinated in high dilutions, not even a 1:20 dilution produced an agglutination of the paratyphoid bacilli. In two cases I observed an agglutination of paratyphoid type B with a dilution 1:40, while typhoid bacilli were agglutinated with 1:300 and over. In the cases reported by JÜRGENS,[2] however, the paratyphoid bacilli were agglutinated by the typhoid serum in every case excepting one. Similar results were obtained by this author in his previous study in conjunction with CONRADI and

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[1] *Zeitschrift für Hygiene und Infectionskrankheiten* 1902.

[2] Beobachtungen über die Widal'schen Reaktion und die Mitagglutination der Typhoid-bacillen. *Zeitschrift für Hygiene und Infectionskrankheiten* VI, 1903.

von Drigalski.[1] Recently Korte [2] also has frequently observed that typhoid sera agglutinate not only typhoid bacilli, but also one or both varieties of paratyphoid, even when a simultaneous infection with paratyphoid was excluded. This agglutination for the other bacilli was in some cases quite marked, though there was no uniformity whatever. Since he found that, conversely, in paratyphoid infection the serum possesses a fairly strong agglutinating action on typhoid bacilli, Korte advises that in every case of typhoid all three bacteria be tested for agglutination, so that, according to the strongest agglutinating action, one can decide which infection is present. If in practice it is immaterial whether this point be decided, the agglutination with paratyphoid need only be undertaken when the typhoid agglutination is absent.

In all this we are dealing with the same phenomenon which undoubtedly plays a rôle in the agglutination with blood of icteric patients, the so-called *group agglutination*, as it was first termed by Meinhard Pfaundler.[3] This is based on the fact already mentioned, that in an infection not only the infect-

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[1] l. c.

[2] *Centralblatt für Hygiene und Infectionskrankheiten*, Vol. XLIV, 1903, p. 243.

[3] Über Gruppenagglutination und das Verhalten des Bacterium coli bei Typhus, *Muench. med. Wochenschrift* 1899, No. 15.

ing micro-organism but frequently also other bacteria are agglutinated by the serum. In other words, the agglutinins are not strictly specific antibodies. As a rule the agglutination with the infecting agent is by far the strongest, i.e. it proceeds even in high dilutions, whereas other bacteria require a stronger concentration. The bacteria which are agglutinated by one and the same serum need not at all be related in their morphological or other biological characteristics, as PFAUNDLER at first assumed. Conversely, micro-organisms which, because of the characteristics mentioned, are regarded as entirely identical or almost so, are sharply differentiated by means of their agglutination. In other words, the "groups" arrived at by means of a common agglutination have no relation to species as the term is usually employed. Thus, according to STERN, certain varieties of proteus and of staphylococci excite the production of sera which exert marked agglutinating powers also on typhoid bacilli, although otherwise we do not regard these three micro-organisms as at all related. On the other hand by means of agglutination we can sharply distinguish cholera bacilli from their nearest related species. Because of this lack of absolute specificity the *serum diagnosis of bacteria* has in certain instances lost much of its value. Where formerly, for example, a doubtful bacillus was regarded as positively a

typhoid bacillus if it was agglutinated by typhoid-immune serum, we now know, owing to the researches of STERN,[1] BIEBERSTEIN,[2] and others, that coli groups in some cases are agglutinated by typhoid-immune serum even more strongly than typhoid bacilli themselves. It is therefore impossible to say whether a certain bacillus is that of typhoid or coli if we merely know that it is agglutinated by typhoid serum. The observations of JÜRGENS [3] are analogous to those of the above-named authors. In one case he found that the paratyphoid bacilli were agglutinated more strongly than the typhoid bacilli, although only the latter could be demonstrated in the spleen.

Besides this mere "group agglutination" we must bear in mind that there can be a mixed infection, i.e. the serum of an individual may agglutinate two kinds of bacteria, because there is an infection with both kinds. A number of cases of simultaneous infection with typhoid and paratyphoid bacilli have been described. As a rule, in these cases the agglutinating values are not so far apart as in the case of mere group agglutination. In order to decide whether merely group agglutination exists or whether there is a mixed infec-

[1] *Centralblatt für Bacteriologie*, Vol. XXIII, 1898.

[2] *Zeitschr. für Hygiene und Infectionskrankheiten*, Vol. XXVII, 1898.

[3] l. c., page 390.

tion we make use of the procedure devised by CASTELLANI.[1] This is as follows: To the diluted immune serum successive quantities of the bacilli most strongly agglutinated are added until the agglutinating power of the serum for these organisms = 0. The tube containing this mixture is then placed in the refrigerator so that the supernatant fluid becomes fairly clear. Then the second variety of bacteria is added. If a mixed infection is present, these bacteria will be agglutinated as strongly as ever, whereas if there was merely a group agglutination, they will no longer be agglutinated, for the agglutinin has been neutralized by the bacteria with the greatest affinity.

Résumé. — Reviewing the experiences we now possess on the serum diagnosis of typhoid fever, we may summarize these as follows: The presence or absence of the GRUBER-WIDAL reaction does not positively speak for or against the presence of typhoid. All recent authors, especially STERN, therefore now insist that the value of the GRUBER-WIDAL reaction in diagnosis is only that of a clinical symptom. Nevertheless, according to my experience, it is a symptom which, because of its importance, *must be ranked first of the cardinal symptoms of typhoid.* It certainly possesses much

[1] Die Agglutination bei gemischte Infectionen, etc. *Zeitschr. für Hygiene und Infectionskrankheiten*, Vol. XL, 1902.

more diagnostic value than any other symptom (fever, splenic enlargement, roseola, pulse, diazo reaction, etc.). It is the more important because in some cases it appears earlier than the other classic symptoms and because it usually remains for months after the subsidence of the fever. In the diagnosis of a previous typhoid, in some circumstances of considerable interest, the reaction very soon becomes the only means at our disposal; for, although the demonstration of typhoid bacilli in the fæces or urine is possible a short time after the subsidence of the fever, after a few weeks this is no longer so. Owing to its value the GRUBER-WIDAL reaction has secured a permanent position among the diagnostic measures of the physician. It must not, however, be forgotten that it is not at all equal in value to the direct demonstration of typhoid bacilli. This is especially the case when one wishes in large epidemics to determine whether slightly ill or apparently healthy persons are infected with typhoid or not. In these cases the GRUBER-WIDAL reaction should not be relied upon, but one should proceed to isolate the bacteria from the fæces by means of a suitable nutrient medium (litmus and lactose agar devised by v. DRIGALSKI and CONRADI [1]). If the experience of JÜRGENS

[1] *Zeitschrift für Hygiene und Infectionskrankheiten* 1902, p. 283.

proves generally applicable, it is just in these patients that a strong agglutinating action is rarely found. Finally, I should like to emphasize once more that, according to my views, the reaction is only then to be regarded as completely performed when, if the reaction is negative, it is undertaken also with paratyphoid.

Ficker's Typhoid Diagnostic.—In the fall of 1903, FICKER[1] reported a new method of serum diagnosis for typhoid fever. His test, a modification of the GRUBER-WIDAL reaction, does away with living bacilli and with the microscope, besides requiring only a short time. The test can therefore readily be made by any physician in his office. The *Typhoid Diagnostic* prepared by MERCK & Co., according to the instructions of Dr. FICKER, consists of a specially treated and sterilized typhoid culture which serves for carrying out the GRUBER-WIDAL reaction. It is accompanied by all the apparatus necessary for performing the test.

The reaction is made with *blood-serum*, and a number of procedures have been suggested to obtain this. One of the simplest methods is that recommended by ROSTOSKI.[2] CLAMANN[3] advises that the blood be abstracted directly from a vein.

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[1] *Berliner klin. Wochenschrift* 1903, No. 45.

[2] See page 18.

[3] *Deutsche med. Wochenschrift*, July 7, 1904.

He makes use of a hypodermic syringe without a needle, which should be of a pattern which permits ready sterilization by boiling. After the syringe is filled with about one c.c. of blood as it flows from the wound, the opening may be closed with sterile wax or a small rubber cap, and the instrument transported to the laboratory. When ready to make the test, the piston is slightly withdrawn, liberating the clot and allowing the serum contained in the barrel to find its way out.

The directions given by FICKER are as follows:

1. *Taking the blood specimen.* After the cupping-glass, rubber stopper, and lancet have been sterilized by boiling in water, the lumbar region of the patient, who is placed in a sitting posture or reclining on one side, is cleansed with soap and water, alcohol and ether. Three to four rather deep incisions quite close together are then made with the lancet, and the cupping-glass applied in the usual manner. When about 1 c.c. of blood has been drawn, the cupping-glass is removed, closed with the rubber stopper, and set aside in a cool place until the serum has separated.

2. *Carrying out the test.* The pipette and test-glasses must be cleansed by washing with alcohol and ether; the stoppers of the test-glasses are sterilized by boiling with water.

0.1 c.c. of the serum, which must be perfectly

free from blood-corpuscles, is introduced into a test-glass by means of the pipette, with which, after it has again been washed with water, alcohol, and ether, 0.9 c.c. of the sterilized sodium-chloride solution is then added to the serum. The sterilized stopper is now inserted, and the liquid thoroughly mixed. Of this diluted serum 0.1 c.c. is placed in a second test-glass, and 0.2 c.c. in a third. With the pipette, which is then again washed as above, 0.9 c.c. of the previously thoroughly shaken diagnostic reagent is transferred to the second test-glass, and 0.8 c.c. to the third. The serum dilution in the second glass will hence be 1 : 100, while that in the third glass will be 1 : 50. One c.c. of the diagnostic reagent is now transferred to a fourth glass. All the glasses are then stoppered with the previously boiled stoppers, thoroughly shaken, and allowed to remain at rest in the stand at room temperature, and protected from light. In most cases the reaction is distinctly visible in from 10 to 12 hours. A longer period than 20 hours must not be waited in order to make certain of the result. The reaction is *positive* when the bacteria present in the diagnostic liquid conglutinate and sink to the bottom, while the liquid contents of the glass become clear. The beginning of the clarification is best seen when the glass is observed in a good light with a dark background, and compared with the fourth test-glass

containing only the diagnostic liquid; or by raising the glass to the level of the eye with one hand, while the other hand, held 5 to 10 cm. behind the glass, but between this and the source of light (window), is gently moved to and fro.

J. MEYER,[1] working under the direction of Prof. HANSEMANN in Berlin, reports the reaction as even more reliable than the GRUBER-WIDAL. In two cases in which the latter was doubtful, the FICKER test gave a positive result. EHRSAM [2] reports on five cases of typhoid in LEUBUSCHER'S infirmary in Meiningen, in which positive results were obtained in every case in the third week and in convalescence. DATTA [3] found that the reaction gave results exactly parallel to those obtained by the GRUBER-WIDAL method. In the twelve cases examined by him the reaction was tried by both the methods of FICKER and WIDAL, and whenever the reaction could not be obtained by one method it was absent when the other was applied. v. ELJASZ RADZIKOWSKI [4] and likewise KASARINOF [5] also report favorable results with this reaction. LION,[6] working in the Würzburg clinic, has recently subjected

[1] *Berliner klin. Wochenschrift*, 1904, No. 7.
[2] *Muench. med. Wochenschrift*, 1904, No. 15.
[3] *Gazetta degli Ospedali e delle Cliniche*, March 13, 1904.
[4] *Wiener klin. Wochenschrift*, 1904, No. 10.
[5] *Russkji Wratsch*, 1903, No. 51.
[6] *Muench. med. Wochenschrift*, 1904, No. 21.

FICKER'S REACTION to thorough comparative tests. His results lead him to speak very highly of the method. He calls attention to the fact that the time limit must not be more than twenty hours; after twenty-four hours a precipitate may be formed even with normal serum (1 : 20). He concludes as follows: ". . . The practitioner would therefore be glad to have a fluid which always assures the same composition, and therefore always ready for use. Furthermore, if such a 'reagent' were not infectious, this would be an advantage that could not be overestimated. FICKER'S typhoid diagnostic and also the 'formalin typhoid cultures' have proven themselves to be such reagents and to be absolutely trustworthy. Since the latter is in every way as efficacious as the former, and can be prepared by the physician himself without difficulty or expense, I cannot too highly recommend the test with formalin cultures."

The Test with Formalin Cultures. — As already mentioned,[1] WIDAL and PROESCHER have recommended the employment of typhoid cultures killed with formalin. According to ROSTOSKI,[2] these are prepared as follows: To a well-grown (24–48 hours) bouillon culture of typhoid, one per cent formalin (*Formaldehydum solut.* Pharmacop. Ger-

[1] See page 13.

[2] Personal communication. [BOLDUAN.]

manica IV = 35% formaldehyde) is added. The test-tube is well stoppered and a precipitate which forms in the course of the following week allowed to settle, or this may be removed by filtering through ordinary filter-paper. In this way a suspension of dead bacteria is obtained which will keep for months.

Working with this, the test can be performed either macroscopically, or microscopically in the hanging drop. The dead cultures are in every way equal to the living cultures except in one respect, that the reaction takes longer to develop. This is true for the macroscopic as well as for the microscopic method, so that the time limits must be greater than when living cultures are used. LION'S [1] experiments show that, in regard to distinctness and time required, the results obtained with the formalin cultures are almost entirely identical with those of FICKER'S diagnostic. In all positive cases the reaction commenced promptly and was completed in from 2–20 hours.

LION also studied the behavior of formalin cultures of paratyphoid types A and B, with typhoid and paratyphoid sera, and found that such cultures could be used in the same manner as the preceding. He emphasizes the recommendation

[1] *Muench. med. Wochenschrift*, 1904, No. 21.

of Rostoski that one always have on hand a mixed formalin culture of both types of paratyphoid bacilli. In suspicious typhoid cases the test is first made with the typhoid formalin bouillon; if this is negative, the test is made with the mixture. The diagnosis can then further be specialized by means of formalin bouillon of paratyphoid A and of paratyphoid B.

CHAPTER III.

TUBERCULOSIS.

The Arloing-Courmont Reaction.—At the present time the serum diagnosis of tuberculosis is to be looked upon as rather unpromising. It was brought forward by ARLOING [1] in 1898 and later was thoroughly studied especially by COURMONT and other French authors. Since the tubercle bacilli in an ordinary bouillon culture already lie in clumps, it is first necessary, in order to attempt an agglutinating reaction, to prepare a homogeneous, i.e. uniformly clouded, culture. For this purpose ARLOING and COURMONT grow a culture of tubercle bacilli on potatoes, plant from this into 6% glycerin-bouillon, and shake the latter cultures several times daily in order to distribute the little groups. After several generations the cultures will be found to have become homogeneous. With this change in growth, the culture has also acquired other prop-

[1] A comprehensive review of the literature on this subject will be found in Eisenberg and Keller, Über die Spezifität der Serodiagnostik der Tuberculose. *Centralblatt für Bacteriologie*, Part I, Vol. XXXIII, 1903, No. 7.

erties. The separate bacteria present the greatest variety of form; their resistance to acid and, above all, their pathogenicity subsides. When such a culture is injected into animals, only local cheesy lesions are formed; the tendency to a general infection is absent. A number of German investigators have also succeeded in producing such homoge, neous cultures of tubercle bacilli; others, however report failures. In that case they have used the original cultures of ARLOING-COURMONT.

After the serum to be tested has been properly diluted, it is added to a 7–12-day homogeneous culture of tubercle bacilli. Then, preferably in a hanging-drop preparation, one sees whether the bacteria have been agglutinated. According to ARLOING and COURMONT, the lowest limit which can be used for diagnostic purposes is a dilution of 1:5. Positive reactions have, however, been obtained in dilutions of 1:500 and 1:600. The French authors claim that the reaction is particularly valuable (1) for the diagnosis of beginning phthisis in man (during the later stages of human phthisis the reaction is said to be less frequently observed, because the enfeebled organism no longer produces sufficient antibodies); (2) for the diagnosis of bovine tuberculosis. In the latter field, the French authors believe that the reaction will displace KOCH'S tuberculin test. Their results

are so favorable that the serum diagnosis has failed only once in 120 animals, whereas in the most favorable case one must always reckon with an error of 2% in KOCH'S reaction.

It is to be regretted that the experiences of others, especially of the German investigators, are not nearly so favorable as those of the French. Only the work of BENDIX [1] in LEYDEN'S clinic is an unqualified endorsement of the method. In thirty-six cases of tuberculosis BENDIX obtained a positive reaction thirty-four times; in six non-tuberculous cases, only negative results. BECK, RABINOWITSCH,[2] DIEUDONNÉ,[3] and many others observed, however, that the reaction was absent in many cases of proven tuberculosis, and that numerous healthy individuals show the reaction. Above all, the results of BECK and RABINOWITSCH speak strongly against the reliability of the method. Their investigations were made on 78 cattle which were afterwards slaughtered. This gave them the opportunity to determine by direct observation whether or not the animals were tubercular. Their report

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[1] Zur Serodiagnose der Tuberculose, *Deutsch. med. Wochenschr.* 1900, No. 14.

[2] *Zeitschrift für Hygiene und Infectionskrankheiten,* Vol. XXXVII, 1901, p. 205. *Deutsche med. Wochenschrift* 1901, No. 10.

[3] Zur Frühdiagnose der Tuberculose, *Deutsche Militärärztliche Zeitschrift* 1900, No. 10.

shows that the percentage of positive reactions was the same in the tubercular as in the non-tubercular cattle. The statistics of EISENBERG and KELLER, which deal only with cases coming to autopsy, deserve special mention. In twenty tubercular cases these authors found 71.5% positive and 28.5% negative reactions; in fifty-three non-tubercular, 70% positive and 30% negative. That is, the figures for the tubercular and the non-tubercular are almost equal, and hence speak strongly against the specificity of the serum reaction. Even when one assumes that, despite careful examination, a tubercular scar or gland may now and then be overlooked, though the disagreement between positive reactions and tubercular and non-tubercular cases may be somewhat lessened, *the specificity of the reaction can no longer be maintained.*

ROMBERG [1] recently showed that the serum of thirty-three new-born did not agglutinate cultures of tubercle bacilli even with dilutions of 1:1, and RUITINGER [2] publishes the same results for five new-born. We can therefore believe that human serum at the outset never agglutinates, and that every

[1] Weitere Untersuchungen zur Serumdiagnose der Tuberculose, *Muench. med. Wochenschrift* 1902, No. 3.

[2] Zur Serumdiagnose der Tuberculose, *Zeitschrift für Tuberculose und Heilstättenwesen.* Vol. III, 1902, No. 6.

agglutination later in life is caused by the absorption of the tubercular poison or by the presence of ever so small a tubercular lesion. The statistics of NAEGELI, which include 500 cases, have shown that 98% of all adult bodies coming to autopsy show tubercular lesions. However, even if it should be proven that every positive reaction is caused by the presence of a tubercular lesion, the ARLOING-COURMONT test would gain nothing thereby, for it is equally certain that numerous cases of tuberculosis exist whose serum does not agglutinate. Furthermore, the reaction may lead to a wrong diagnosis, for an entirely insignificant tubercular lesion may exist along with a pathological process whose etiology is not at all clear. A positive serum reaction might then cause the symptoms to be declared tubercular. Hence ROMBERG, while he maintains the specificity of the reaction, refuses to accept its diagnostic significance.

The varying percentage of positive reactions obtained by different authors in known cases of tuberculosis is very surprising. Thus ARLOING and COURMONT report 94% positive reactions; BENDIX, 81%; BECK and RABINOWITSCH, 31%; FRAENKEL, 27%. It is possible that these divergent results may be explained by the use of different kinds of cultures. It is known that in typhoid there are slight differences in the agglutinating

powers of different cultures. In tuberculosis these differences are doubtless considerable. Fully virulent, not too closely grown cultures are best agglutinated. In order always to have a uniform culture material, v. BEHRING has proposed an emulsion made of dead bacteria, since, according to his investigations, these agglutinate just as dead typhoid bacilli agglutinate with typhoid immune serum. However, as I am able to learn from the literature, we thus far possess too little material on which to base any conclusions concerning the value of the method.

Koch's Test.—ROBERT KOCH,[1] who, by the way, also considers the agglutination test valueless for purposes of diagnosis, makes use of the bodies of bacteria ground in a mill for an agglutination test. These same bacteria are also used in the preparation of turberculin (T. R.), and can at any time be obtained from the firm "Farbwerke Höchst." An extract is made from these bacterial bodies of the strength of 1 : 10,000, according to the directions accompanying each package. This is filtered and mixed with the particular dilution of the tubercular serum. In cases of a positive reaction a precipitate is noticed, the soluble substance of the bacterial bodies having

[1] Ueber die Agglutination der Tuberkelbazillen und über die Verwertung dieser Agglutination. *Deutsch. med. Wochenschr.* 1901, No. 48.

been precipitated and clumped into little flakes by the active serum. As already stated, KOCH does not use this reaction for diagnosis, but only in order to learn how strong a certain serum is in protective bodies, and how far this can be increased by the injection of tuberculin. Through his animal experiments KOCH has come to the conclusion that in tuberculosis the degree of agglutinating action of the serum, furnishes a measure of the bactericidal and antitoxic action of the same.

CHAPTER IV.

AGGLUTINATION IN OTHER DISEASES.

Bubonic Plague.—In this disease[1] also the serum contains specific agglutinating substances, whereas normal blood-serum never agglutinates plague bacilli, not even in the proportion 1 : 1. Nevertheless the agglutinins are unavailable for the diagnosis of plague, for they do not develop until the second week, a period of the disease at which the diagnosis can be made beyond question by means of other symptoms. In some cases the agglutinins do not develop until convalescence. The agglutinating power of the serum reaches its maximum about six or seven weeks after the illness, as was shown by CAIRUS, and it usually disappears after five months. Furthermore, the reaction is absent in a large number of cases, and finally the serum is usually efficient only in dilutions of 1 : 5, although now and then agglutination is observed in dilutions of 1 : 100. According to DIEUDONNÉ,[2] the serum

[1] See Dieudonné in Handbuch der pathogenen Microorganismen by KOLLE and WASSERMANN, p. 525.

[2] l. c.

diagnosis can then perhaps have some value if it is desired to diagnosticate a case which has already run its course. Even then, however, only a positive reaction possesses any value; a negative reaction does not exclude plague.

MARKL, KOLLE, and MARTINI have demonstrated that the agglutinating action of plague serum is strictly specific; a "group agglutination" with other closely related bacteria, such as those of chicken-cholera, does not occur. Hence plague serum can be used to advantage for the identification of plague bacilli. In order to obtain the plague-immune serum it is best to immunize a horse. Such a serum possesses a much higher agglutinating power than the serum of plague convalescents. In some cases such a serum has been found active even in dilutions of 1:5000 to 1:6000. This agglutinating method of identification is especially valuable for cultures which are no longer virulent, for in that case identification by means of animal experiments fails.

Asiatic Cholera. — In this disease the agglutination reaction possesses the same value as in bubonic plague. It is valuable for the identification of the excitant of the disease, but not for the direct diagnosis of the disease itself. One may, of course, examine suspicious cases of cholera after these have run their course, observing the behavior of their

blood-serum on a known fresh culture of cholera bacilli. If the serum possesses a high agglutinating power, the diagnosis of a previous cholera can be made. I have been unable in the recent literature to find any more definite statements concerning the period in the disease when the agglutinins develop, how long they remain in the blood, how strong the agglutinating power becomes, etc. Nowadays the positive diagnosis of cholera is effected solely and only by the demonstration of cholera bacilli in the dejecta of the patients. In identifying the bacilli thus cultivated, PFEIFFER'S reaction, mentioned below, and the agglutination test are most important. During the cholera epidemic in Egypt in 1902, W. KOLLE and E. GOTTSCHLICH[1] were able to determine that the agglutination test is extremely reliable in the identification of cholera bacilli. On the one hand all cultures of cholera are agglutinated by the serum of an animal into which any one of the cholera cultures are injected; never, however, are cholera-like bacilli agglutinated by such a serum. On the other hand it is impossible by injecting the cholera-like bacilli to produce a serum which will agglutinate true cholera bacilli. KOLLE and GOTTSCHLICH describe a highly ag-

[1] Untersuchungen über die bacteriologische Choleradiagnostik und Specifität des Koch'schen Cholera Vibrio, *Zeitschrift für Hygiene und Infectionskrankheiten* 1903, Vol. XLIV, No. 1.

glutinating horse-serum which acts on cholera bacilli even in dilutions of 1:20,000, whereas a dilution of 1:100 shows not the slightest action on the cholera-like bacilli. As in the case of plague, group agglutinations do not seem to occur in cholera. Hence in the "Decree of the Prussian Department of Public Health, Nov. 6, 1902," [1] the agglutination reaction has been given as one of the tests to determine the identity of the cholera bacillus. According to KOLLE and GOTTSCHLICH, a serum possessing high agglutinating properties is best prepared by immunizing rabbits or asses, whose serum as such possesses but little agglutinating power for cholera bacilli, whereas the sera of other animals even normally agglutinates cholera bacilli in moderate dilutions. It is best to employ intravenous injections of dead bacilli. Such a cholera serum can be obtained from the *Royal Institute for Infectious Diseases, Berlin.* Since such a serum loses some of its agglutinating power on standing, the recommendation of KOLLE [2] to dry it carefully in vacuo has been followed. The result is a readily soluble crystalline powder occupying one-tenth the volume of the fluid serum. The powder must therefore be dissolved

[1] This decree was formulated by R. Koch, Kirchner, and Kolle. Compare W. Kolle in Handbuch der pathogenen Microorganismen by Kolle and Wassermann, Vol. II. page 45.

[2] *Klinisches Jahrbuch* 1903, Vol. XI, No. 3, page 392.

in nine volumes of 0.85% salt solution before being used. Such a dry serum retains its agglutinating power certainly for months, but probably for over a year. Concerning the method recommended by KOLLE for the agglutination of cholera bacilli, see under "MENINGOCCOCUS," page 63.

In the identification of cholera bacilli a specific *bacteriolysin* can also be employed, and in this connection the bacteriolysins are probably of greatest value. The way in which PFEIFFER's phenomenon proceeds has already been described (see page 3). I should merely like to add that this reaction is fully equal in value to the agglutination test because of the highly marked specificity of the cholera bacteriolysins. For this reason this reaction is included in the tests for identifying the cholera bacilli given in the above-mentioned government decree. The method of making the test is fully described in KOLLE's article on "Asiatic Cholera" in KOLLE and WASSERMANN's handbook of pathogenic micro-organisms.

Dysentery and Para-Dysentery.—In bacillary dysentery (as distinguished from amœbic) it has been found that there is an agglutination by the serum of the excitant of the disease, the *dysentery bacillus* discovered by SHIGA and KRUSE. The reaction, however, is not constant, and, especially in severe cases, is frequently absent. Hence only

a positive reaction is to be considered diagnostic. Furthermore, since the reaction, according to SHIGA, does not appear before the seventh day, it has little value for the diagnosis of the disease, for by that time the clinical picture will have determined the diagnosis. However, in doubtful cases which are already convalescing, the reaction may serve good purpose.[1]

In the identification of the dysentery bacillus, on the other hand, the agglutination test has proven of considerable value. According to MARTINI and LENTZ,[2] it is best for this purpose to use an artificially produced high-grade animal serum, since the sera of convalescents may also agglutinate related bacteria. By means of such a serum it has been found that the dysentery bacilli from different parts of the world are agglutinated by the same serum, while related species are not agglutinated. A few dysentery bacilli isolated in the Philippines were, however, not agglutinated, and it is still questionable whether these are the true excitants of the disease and not saprophytes.[3] MARTINI

[1] O. Lentz on "Dysentery" in Kolle and Wassermann's handbook.

[2] *Zeitschrift f. Hygiene und Infectionskrankheiten* 1902, No. 41.

[3] TRANSLATOR'S NOTE: The most recent work on this subject has been done by W. H. PARK. (Park, Collins, and Goodwin, *Journ. of Medical Research*, May 1904, pp. 553–568). This author shows that the great majority of bacilli which have been isolated from cases of dysentery not due to amœba, and

and LENTZ recommend KOLLE's macroscopic method as being especially adapted to the agglutination test with dysentery bacilli. (Compare Agglutination of the Meningococcus, page 63.)

Glanders. — In glanders also, according to the researches of KLEINE,[1] the agglutination reaction

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which must be considered as being exciting factors in that disease, are included in three distinct varieties.

The type most frequently found in severe epidemics is that of the first culture isolated by SHIGA, which is characterized among other features by the fact that it does not ferment mannite. Animals injected with it produce specific agglutinins for this type in abundance, and only very little that combines with the others.

The second type ferments mannite with the production of acid, but does not split maltose or saccharose in peptone solution or agar. Animals inoculated with it develop immune bodies and agglutinins specific for this type. They also develop in considerable proportions immune bodies and agglutinins which have affinity for the bacilli of type III and to a less extent for type I.

The third type, to which belongs the original Philippine culture isolated by FLEXNER and STRONG, is nearest the colon group, since it not only produces indol and actively ferments mannite, but also acts energetically upon maltose and feebly upon saccharose. Animals injected with this type develop specific immune bodies and agglutinins, and also abundant immune bodies and agglutinins which have an affinity for the bacilli of type II and for many bacilli of the colon group. For type I these substances are but slightly developed.

PARK concludes that it would be more convenient to restrict the name *dysentery* to bacilli having the characteristics of the bacillus isolated by SHIGA, and give the name *para-dysentery* to the other two groups. An additional reason for the use of the prefix *para*, beyond that of convenience, is the less average severity of the disease due to these types.

[1] *Zeitschr. für Hygiene und Infectionskrankheiten*, Vol. XXIV, No. 2, 1903.

has proven of value in the identification of the bacterium.

Pneumococcus Infection.—Up to the present time, the agglutination reaction possesses little practical significance in this condition. It has been studied especially by BESANÇON and GRIFFON, HUBER, NEUFELD,[1] and JEHLE.[2] Agglutination has been observed in the serum of infected animals, and without exception in the serum of patients suffering from pneumococcus pneumonia. In the latter it is frequently noticed as early as the third or fourth day of disease, most often, however, just before the crisis, and it disappears after several weeks. According to JEHLE, the reaction in children persists only about four days after the crisis, but appears early. This behavior is analogous to that of the agglutination phenomenon of typhoid in children, in which, as already mentioned, the reaction also rapidly disappears from the blood-serum. *This reaction, therefore, can be employed as a diagnostic aid in those cases in which the direct demonstration of pneumococci, e.g. in the sputum, does not succeed, but in which, nevertheless, it is sought to determine whether the infection is due to pneumo-*

[1] Compare F. Marx, Diagnostik, Serumtherapie und Prophylaxe der Infectionskrankheiten, Coler, Vol. XI. p. 189. Also A. Weichselbaum in Kolle und Wassermann's Handbuch der pathogenen Microorganismen, p. 199.

[2] *Wiener klin. Wochenschrift* 1903, No. 32.

cocci or to other bacteria. It seems to me that investigations in this direction are distinctly advisable. According to our experiences thus far, this agglutination is a constant phenomenon in pneumococcus pneumonia, and therefore very likely also in other pneumococcus infections. In the differentiation of several varieties of pneumococci, and especially in the sometimes difficult separation of this from streptococcus pyogenes, the agglutination test possesses but little value. According to NEUFELD'S investigations, this is because the reaction fails with less highly virulent varieties.

Because of this fact it is essential that no avirulent culture be used in the examination of blood-serum of pneumonia patients. The method of examination recommended by BESANÇON and GRIFFON is as follows: Pneumococci are inoculated into the diluted or undiluted serum from the patient, and also into normal blood-serum. Fifteen to twenty-four hours later the normal serum shows a uniform clouding, and in a stained microscopic preparation, pronounced diplococcus formation and very little chain formation. In the other serum, in case of pneumococcus infection, there is a marked precipitate, and above this a clear fluid. The microscopic preparation shows long chains (of twenty or more members) clumped together. If the serum is less active, the fluid remains clouded, but the

microscope shows the same long chains. The method requires careful attention to aseptic details.

Meningococcus Infection. — In regard to these micro-organisms we know from the animal experiments of JAEGER[1] that cultures from various sources are agglutinated in the same manner by a high-grade rabbit-serum, but that related bacteria are not agglutinated by this. Hence in the future the agglutination test must be considered at least in the identification of the excitant of epidemic cerebro-spinal meningitis. It has not yet been determined whether such patients produce sufficient agglutinin to enable the disease to be diagnosticated by means of a culture of meningococcus; nor do we know at what time these agglutinins develop. Both questions must be left to subsequent investigations. I wish now briefly to sketch the method employed by JAEGER. According to this, the serum is diluted with 0.85% salt solution which has been previously filtered through dense (hardened) filter-paper. A number of different dilutions are thus prepared, 1 c.c. of each of which is placed into a test-tube. Thereupon one loop of a 24-hour agar culture is rubbed up on the wall of each tube and then uniformly mixed by shaking. After allowing these tubes to remain in the thermostat

[1] *Zeitschr. für Hygiene und Infectionskrankheiten*, Vol. XLII, No. 2, 1903.

for one hour or more, they are taken out and examined. This is best effected by holding the tubes slantingly and examining them with a low magnifying-glass. This method has the advantage in that the same amount of culture, one loop, is always employed. It is now generally used in the Institute for Infectious Diseases (for example, for cholera diagnosis, KOLLE and GOTTSCHLICH). For typhoid agglutination the microscopic test has thus far been preferred to the macroscopic, such as this, and I have therefore described the former at length under "Typhoid," page 11. It is a method which I have found valuable in many years' work. However, I believe that with careful technique excellent results will be achieved with both methods. To be sure, the limits of agglutination may fluctuate somewhat in the two methods, and it would perhaps be advisable in a given series of experiments always to employ the same method.

Streptococcus Infection.—This has recently been the subject of a number of studies, of which several have been concerned with the question whether the streptococci found in scarlet-fever deserve a distinct place, and whether they are directly related, ætiologically, to the disease. HASENKNOPF and SALGE,[1] using the method recommended by R. KOCH for

[1] *Jahrbuch für Kinderheilkunde*, Vol. LVIII, Aug. 1, 1903. See also the earlier literature.

tuberculosis (see page 47), found that scarlet-fever serum invariably agglutinated scarlet-fever streptococci during the disease. Streptococci of other origins, on the contrary, with one exception, were not agglutinated. Furthermore, the sera of two patients infected with streptococci, namely, an erysipelas serum and the serum of a septic case, did not agglutinate the scarlet-fever streptococci. F. NEUFELD,[1] however, succeeded in agglutinating with the same animal serum a large number of different kinds of streptococci (among them various scarlet-fever streptococci) by removing the differences in their virulence. The agglutinating capacity was dependent on the degree of virulence in this wise, that weakened cultures, as a rule, were much more strongly agglutinated than fully virulent cultures. Besides this, as other authors have already shown, the agglutinating capacity of streptococci derived from man is changed by passage through animals. Hence we are not permitted to assign a distinct place to scarlet-fever streptococci merely because of their agglutination. Altogether the serum identification of streptococci as well as serum diagnosis of streptococcus infections has so far achieved very little.

Staphylococcus Infections.—Unlike the results ob-

[1] *Zeitschrift für Hygiene*, Vol. XLIV, No. 2, 1903, p. 161.

tained with streptococci, the serum diagnosis of staphylococci seems of some value. KOLLE and OTTO,[1] by animal immunization, have produced sera which agglutinated cultures of *staphylococcus aureus*, and *albus* derived from abscesses and phlegmons, in a specific manner. Other cocci, on the contrary, were not agglutinated, even though morphologically and culturally exactly similar to the pyogenic staphylococci.

Résumé.—If we glance over the work thus far accomplished in the diagnostic field, and leave out of account typhoid, which we have already discussed, we see that the agglutination reaction has, without doubt, proven of value in a number of cases (especially cholera and plague) *in the identification of the excitant of the disease.* Through this, of course, the diagnosis of these diseases has indirectly gained a great deal. *The direct diagnosis of the individual case of sickness, by means of the agglutinating action of the patient's serum (and this would have been particularly valuable to the physician), has not, however, kept pace with the diagnosis just mentioned.* Without doubt the method is of great value in single instances in which a diagnosis is desired after the disease has run its course (plague, cholera, dysentery,

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[1] *Zeitschr. für Hygiene und Infectionskrankheiten*, Vol. XLI, 1902.

pneumococcus infections). In other cases it is possible that closer investigation may lead to something that will help us even in the direct diagnosis by means of the agglutinins.

CHAPTER V.

THE PRECIPITINS AS DIAGNOSTIC AGENTS.

The Forensic Blood Test.—We now take up the study of the latest discovered antibodies, the precipitins, and their application in serum diagnosis. Under ordinary circumstances the human body gets its supply of albuminous substances through the gastro-intestinal tract. Here these substances undergo an extensive cleavage, as a result of which the organism builds up anew an albumin molecule peculiar to itself. Only when large amounts of fluid albumin are introduced into the gastro-intestinal tract at once, as was shown by Ascoli, do unchanged molecules of this albumin reach the blood. In like manner we can introduce foreign albuminous substances into the blood by means of subcutaneous, intraperitoneal, and intravenous injections. The organism responds to such introduction of foreign albumins (whose poisonous nature, by the way, has in part been demonstrated) by producing antibodies. The resultant combination has the tendency to precipitate from solution. At least we regularly observe a precipitate when we mix

an active serum with its corresponding albumin solution in a test-tube. For this reason these antibodies have been termed *precipitins*. Attention was first called to them by TCHISTOWITSCH, BORDET and NOLF, and in Germany by WASSERMANN. Their application in forensic blood diagnosis was simultaneously and independently first pointed out by UHLENHUTH,[1] WASSERMANN and SCHÜTZE,[2] and STERN.[3] Subsequent to this a large number of authors, among them especially UHLENHUTH, again helped to develop the new method.

If a rabbit be injected with ox-blood, or ox-blood serum, it will be found that after a number of such injections the rabbit will have developed precipitins for ox-blood; i.e. its serum will thereafter, with dilute solutions of ox-blood, produce first a clouding, then a flocculent mixture, and finally a precipitate. This precipitate is formed only in ox-blood, not in a solution of any other species of blood. Similarly no precipitate is formed when normal rabbit-serum is used. In this way a specific precipitin serum can be obtained for any species of blood. The specificity, however, is not entirely absolute. Above all, this depends upon the strength of the serum, i.e. its degree of activity. This is measured by the dilution

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[1] *Deutsche med. Wochenschrift* 1901, No. 6.
[2] *Berliner klin. Wochenschrift* 1901, No. 7.
[3] *Deutsche med. Wochenschrift* 1901, No. 9.

in which it will still react. Thus a highly active serum, one, for example, which will still give a distinct reaction when diluted 1:1000 or over, will produce a marked precipitate with the serum used to excite its production; whereas, in the serum of other animal species it will produce slighter precipitates or only cloudings. A less highly active serum will likewise cause a marked precipitate in the homologous blood solution, and a slight precipitate or only a clouding, at the most, in a closely related species. For example, the serum of a rabbit which has been treated with sheep-blood produces a marked precipitate in a solution of sheep-blood, a slight precipitate in a goat-blood solution, and a still fainter one in an ox-blood solution. In some instances the two latter will show only a clouding. If we employ a very weak serum, even the cloudings will be absent, and a precipitate is formed only in the sheep-blood solution. If human blood or blood-serum has been injected, the clouding and precipitation will occur most readily (aside, of course, from human-blood solution) in that of apes. In the precipitin reaction, therefore, the relationship of the single animal species is an important factor. This peculiar behavior has first been thoroughly studied by NUTTALL,[1] who made observations on

[1] *British Medical Journal*, 1901, Vol. II, and 1902, Vol. I. See also Nuttall, Blood Immunity and Blood Relationship, 1904. The Macmillan Co., N. Y.

five hundred different animals. As a result of these a weak human-blood antiserum, besides reacting on human blood, causes a clouding only in the blood of anthropoid apes (chimpanzee, gorilla, orang-outang); a stronger serum causes a clouding also in the blood of other monkeys; finally, a very highly active serum reacts with the blood of all the mammalia. In that case, of course, only a faint clouding is produced even after considerable time. NUTTALL also obtained antisera, each of which was specific for one of the large animal classes (birds, reptiles, amphibia). Here, too, the same quantitative differences were noted.

In order to produce an antiserum a large well-developed rabbit is injected intraperitoneally, at intervals of two to three days, with 8–10 c.c. human blood or blood-serum, or that of another animal species. (For the former, placental blood is well adapted.) After five to eight injections, the animal will have produced considerable precipitin. Six days after the last injection the blood is withdrawn from the carotid or jugular, after having previously taken a specimen from the ear-vein and determined the presence of precipitin. If only about 50 c.c. of blood are withdrawn, it is possible to maintain the life of the animal, especially if physiological salt solution is injected. Then the degree of activity of the serum, its "titration,"

is determined. The homologous and several heterologous blood solutions are prepared by extracting the dried blood with physiological salt solution and diluting until these are of a pale yellow color. After filtering, the blood solutions are placed 2 c.c. each, into small test-tubes, and the active serum is then added drop by drop. According to my own experiences the method of injection above described yields an antiserum which, in dilutions of 1:40, or at least 1:10, will cause an immediate clouding in a homologous blood solution. The clouding may take a few minutes to develop, but in either case, after a short time, the mixture becomes flocculent, and after about half an hour the flakes have formed a precipitate at the bottom of the glass. Occasionally the above method results in the formation of very weak or almost inactive serum, which, of course, is not then to be used. Individual factors in the animals undoubtedly play an important rôle, a suggestion first made by UHLENHUTH.

In the forensic blood diagnosis the subjects of the test are usually blood-stains on clothing, and on wood and metal objects. After such a doubtful stain has been dissolved in physiological salt solution one first proceeds to determine that it is really blood. For this purpose TEICHMANN'S test (the production of hæmin crystals), the guaiac test, and the spectroscopic examination are undertaken. This

is of considerable importance, for not merely blood but other albuminous solutions derived from the same animal react with an antiserum obtained by injecting an animal with blood or serum. Having found that the stain is that of blood, we next determine the special kind of blood. For this purpose the blood solution is diluted until it has a pale yellow color and then filtered. Into a small test-tube are placed 2 c.c. of this filtrate, and then by means of a small pipette, dropping twenty drops to the c.c., one to four drops of a 1:40 to 1:10 dilution of the antiserum, are added, depending on its activity. The tubes are shaken and the result noted. Then they are placed into an incubator for half an hour and again observed. A tube of the blood solution to which normal rabbit-serum is added serves as a control test. Naturally the recognition of the particular species of blood will depend on our possession of sufficient different species of antisera. At first, of course, one always tests with human-blood antiserum. If an immediate strong clouding occurs, the diagnosis may be fixed as "human blood." I should like to emphasize that it is essential always to test the activity of the serum beforehand.

Various authors have employed serum of different strengths: KISTER and WOLF,[1] STRUBE,[2]

[1] *Zeitschrift für Medizinalbeamte* 1902, No. 7.
[2] *Deutsche med. Wochenschrift* 1902, No. 24.

SCHULZ,[1] KISTER and WEICHARDT,[2] and others. Usually this was prepared by means of intravenous (ear-vein) injection of the serum in question. Either 10 c.c. were injected three or four times with intervals of several days, or 1 c.c. was injected daily. In making the test the antiserum is diluted to such a degree that it will still cause a marked reaction in the homologous blood solution, but not in other blood solutions, excepting perhaps a faint reaction in the blood of closely related species. Such a dilution is prepared without any difficulty. Hence, according to the opinion of all authors, *the value of the forensic blood test is in no way impaired by the fact that the precipitins are not absolutely specific.* UHLENHUTH, however, is right when he demands that the sera employed be tested under government control.

Several authors prefer very active sera to weaker ones. Probably the only advantage consists in the fact that less material is used. Weaker sera can be used just as well. Thus, UHLENHUTH,[3] working with sera which acted well at 1:40, has made a correct diagnosis in twenty-three medico-legal cases.

If it is desired to completely exclude the action

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[1] *Zeitschrift für Medizinalbeamte* 1902, No. 18.
[2] *Ibid.*, No. 20.
[3] *Deutsche med. Wochenschrift* 1902, No. 37.

on unlike bloods, the procedure suggested by KISTER and WEICHARDT proves useful. By means of this one can prevent the action on one or more unlike species of blood. Thus, a highly active human-blood antiserum may act also on horse-blood solution or horse serum. In order to prevent this action, about 0.5 c.c. horse-serum are added to 5 c.c. of the human-blood antiserum and the resulting precipitate is separated from the clear fluid by centrifuge. This process is repeated several times until the addition of horse-serum no longer produces any precipitate. The resulting serum, even in strong concentration, will not cause any precipitate in horse-blood solution. It will, however, still exert a marked action on human-blood solutions. According to WEICHARDT,[1] it is possible in similar fashion to fix an individual blood diagnosis. For example, a rabbit is injected constantly with blood of one and the same individual (or with blood from a corpse, preserved with phenol). The antiserum derived from this rabbit will then react strongest with the blood solution of the individual (A), and less strong with blood solution of any other individual (B), although the difference is frequently only slight. The difference, however, can be made very apparent if blood-serum of individual B is twice, successively, added to the anti-

[1] *Hygienische Rundschau* 1903, No. 15.

serum and the mixture filtered. The antiserum so treated will act strongly on blood solution of individual A, but only feebly on that of individual B.

The forensic blood test by means of precipitins permits us to correctly recognize blood which has been long dried, subjected to low temperatures or to the action of chemical agents, such as corrosive sublimate, carbolic acid, soap, etc., or which is in process of decomposition. Thus STRASSMANN has correctly identified old blood stains dried on linen since 1883. The blood solution may be very dilute, for the precipitins, according to R. STERN, still act in dilutions of 1:50,000. In practice, to be sure, one will elect to use stronger solutions than this.

The antiserum retains its precipitating power for several months. As a preservative UHLENHUTH and ROSTOSKI have found the addition of chloroform very useful; but a great many other methods of preservation have been recommended, such as the addition of phenol or mercuric chloride, precipitation of the antibodies, together with the albuminous substances, and keeping the dry powder.

In the same way that the species of blood of different animals can be distinguished from each other by means of the precipitins, it is possible to do this with other kinds of albuminous bodies derived from animals (and plants). It has been found that

in general albuminous bodies derived from the same animal react with the same precipitin. For example, an antiserum obtained by injections of ox-blood will precipitate also an extract of the muscle and testes of this animal; not, however, with similar extracts of a different animal. An antiserum obtained by injections of chicken-egg albumin produces a reaction also in chicken-blood, and *vice versa*. In the same manner it is possible to distinguish the different species of milk of the different animals. One thing should be mentioned, namely, that egg-albumin and egg-yolk (UHLENHUTH [1]), as well as casein of milk and lact-albumin of the same species (HAMBURGER,[2] SCHLOSSMANN, and MORO [3]), react to different precipitins. In this case, however, the reaction is still specific for the separate species.

JESS [4] and UHLENHUTH [5] among others have used the biological method particularly in the identification of various kinds of meats. This procedure, for instance, is useful in determining whether chopped meat or sausage-meat is adulterated with cheaper kinds of meat (horse, dog, cat). The same antiserum which is used for the blood test is used.

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[1] *Muench. med. Wochenschrift* 1903, No. 4.
[2] *Wiener klin. Wochenschrift* 1901, No. 49.
[3] *Muench. med. Wochenschrift* 1903, p. 597.
[4] *Berliner thierärztliche Wochenschrift* 1901, No. 42.
[5] *Deutsche med. Wochenschrift* 1901, No. 45.

The albuminous solution is prepared by extracting the sample of meat with chloroform-water or physiological salt solution. Similarly, according to A. Schütze (*Deutsche med. Wochenschrift* 1902, No. 45, and 1903, No. 4), one can distinguish spermatozoa and bones of different animals provided small amounts of albumin are still adherent. This, however, does not by any means exhaust the application of the precipitins to the differentiation of albuminous bodies of different origins. I should, however, like to emphasize again that, *in general, it is impossible to separate the albuminous bodies of the same species from one another by means of the precipitins.*

CHAPTER VI.

OTHER DIAGNOSTIC REACTIONS.

Deutsch's Hæmolytic Test.—Besides the method of blood diagnosis by means of precipitins, a hæmolytic method devised by DEUTSCH [1] may be mentioned. If a rabbit is injected with red blood-cells or blood of another species, its serum will acquire the property of dissolving the red blood-cells of this species in a test-tube, whereas it does not dissolve those of other species. In employing this method one must, above all, have intact blood-corpuscles to work with, a requirement which is unnecessary with the precipitins. For this reason the hæmolytic method has not secured a place beside the precipitin test.

Kraus's Phenomenon.—I return now to a brief account of the fact discovered by KRAUS and already alluded to, that the serum of an animal immunized against typhoid produces a precipitate in a bacterial-free filtrate of a typhoid culture.

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[1] *Centralblatt für Bacteriologie* 1901, Vol. XXIX, No. 16. *Deutsche med. Wochenschrift* 1901, No. 8.

It was natural that this should at once be applied to the diagnosis of typhoid. The great advantages were that one did not need to work with living bacteria, that the filtrate could be prepared and sent out from a central laboratory, and that thus the serum diagnosis of typhoid could find more extensive employment among physicians. The same end was sought by making use of dead bacteria, a method previously mentioned. I regret to say, however, that numerous experiments have taught me that in using the serum of typhoid patients KRAUS's phenomenon often cannot be relied upon. In contrast to this, other experiments with a bacterial-free fluid held out better prospects, especially the method devised by KOCH and carried out by HASENKNOPF and SALGE with scarlatina streptococci (page 64). My own experiments are not yet numerous enough to justify a definite opinion.

APPENDIX.

WILSON'S STUDY ON THE GRUBER-WIDAL REACTION.

In order that one may thoroughly understand what is meant by the term Gruber-Widal reaction, Wilson has prepared a set of drawings, which are here reproduced. His conclusions, which are based on the study of over sixteen hundred blood examinations for the Gruber-Widal reaction, are in part as follows: . . . "In making the hanging drop to be examined it is necessary to have it of such a depth that it will show at least three focal planes (see page 83, Fig. 2), otherwise the examination will be incomplete and unsatisfactory.

"Fig. 1 shows a microscopical field of the *top* of a hanging drop of a normal bouillon culture of typhoid bacilli. This culture is twenty hours old and the organisms are freely motile. This represents the control drop used for comparison with the drop of the same culture, to which has been added a little of the blood of a person

suspected to have typhoid. Note these points in Fig. 1; the organisms are evenly distributed throughout the field, except at the edge of the drop, where they are gathered in great numbers; they show great activity here, seemingly trying to crowd to

FIG. 1.

the very edge. This attraction is probably due to the action exerted on the organisms by the oxygen in the air, which naturally exerts positive chemotaxis on all aerobic organisms.

"Fig. 2 shows a *cross-section* of the drop represented in Fig. 1, and you will notice that the bacilli are evenly distributed throughout the drop, except at one place in the focal plane *a*, and again in the focal plane *c*.

"It sometimes happens that there is something adhering to a supposedly clean cover-glass which

attracts the bacilli to that point where they appear as fairly well defined clumps, more or less like the true clumps due to the agglutinating substance

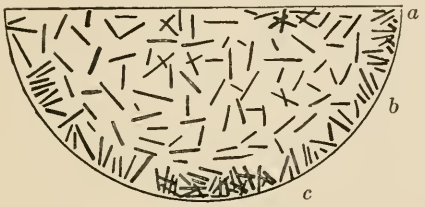

FIG. 2.

in typhoid blood. The increase in organisms at the bottom of the drop in the focal plane *c* is easily accounted for by the fact that gravity naturally carries the dead and non-motile organisms to the bottom, these frequently assuming the character of clumps.

"If you can find a field in any focal plane of the hanging drop free from clumps, you can be quite sure that any clumping present is not due to any agglutinating substance which necessarily will affect organisms in every focal plane.

"Fig. 3 shows the microscopical appearance of the *top* of a drop where the GRUBER-WIDAL reaction is present. Notice first that the organisms have been drawn together in groups and that the individuals of each group appear to be loosely held together. Viewed under the microscope these clumps are practically quiescent, there being very little movement

either of the individual organisms or of the clump as a whole. The edge of the drop is practically

FIG. 3.

free from organisms, showing that the air no longer exerts any influence on them.

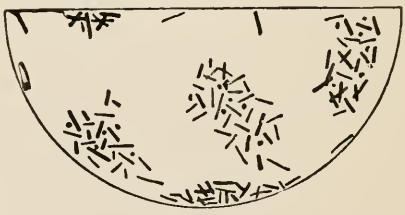

FIG. 4.

"Fig. 4 shows a *cross-section* of the hanging drop shown in Fig. 3. You will notice that the clumps are evenly distributed throughout the drop, with perhaps some increase in the numbers and compactness of the clumps at the bottom.

"Fig. 5 shows the microscopical appearance of the *top* of a hanging drop of a bouillon culture to which has been added some blood of a patient suffering from a febrile condition not caused by typhoid infection, but which exerts a marked influence on the

FIG. 5.

typhoid organisms. You will notice that there are many organisms at the edge of the drop. The air exerts the same influence on the bacilli that it did before the addition of the blood. Note the character of the clumps, generally compact at the center, with the bacilli at the edge of the clump, usually attached by one end only.

"Very frequently these clumps have the appearance of being built up around a piece of detritus present in the clump. All the organisms comprising the clump seem to have retained part, at least,

of their motility, those on the edges being particularly motile, so far as their free ends are concerned. When motility is very much inhibited these clumps have a peculiar trembling movement, which is like the molecular movement described as Brownian.

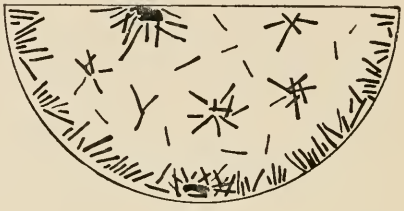

FIG. 6.

" Fig. 6 shows a *cross-section* of the drop represented in Fig. 5. Note the same character of the clumps in every focal plane: the large number of motile bacilli and the number attracted to the edge of the drop by the air. The appearance of the drop shown in Figs. 3 and 4 is what has been taken to constitute a GRUBER-WIDAL reaction in this study, and when any of the characters here shown have been absent the blood has been classed as not giving it. . . ."

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